DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockvlle MD 20857

NDA 18-932/S-013
NDA 18-932/S-014

MAR 05 1999

DuPont Pharmaceuticals Company
Chestnut Run Plaza, Maple Run
974 Centre Road
Wilmington, Delaware 19805

Attention: Maida S. Burka
Director, Regulatory Affairs

Dear Ms. Burka:

Please refer to your supplemental new drug applications (sNDAs) dated March 3 1, 1997 (S-013), and September 2, 1998 (S-014), received April 2,1997 and September 8,1998 respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ReVia (naltrexone HCL) Tablets.

We acknowledge receipt of your submission dated November 23, 1998, (S-014) received November 25,1998.

We note that this supplement was submitted as a "Special Supplement-Changes Being Effected" under 21 CFR 3 14.70(c).

These supplemental new drug applications provide for:

S-013:

-changes in the "Contraindication" section
-an additional "Warning"
-three new "Precautions"
-a more conservative "Impairment of Fertility and Pregnancy" section
-additional **"Adverse Events"**
-and additional guidance to prescribers on the selection of appropriate patients in the "Dosage and Administration" section.

S-014:

-editorial changes providing clarification in the "Description" section
-addition of information in "Warnings" and **"Adverse Reaction" sections** concerning Rapid Detoxification
-rewording of "Carcinogenesis, Mutagenesis and Impairment of Fertility" subsection under the "Precautions" section

-addition of information in the "Adverse Reactions" section concerning use of opioid antagonists associated with a change in baseline levels of some adrenal hormones
-addition of information in the "Overdosage" section.
-changes made to the "How Supplied" section
-replacement of the trade name "NARCAN" with "Naloxone" throughout the labeling.

Your submission stated May 15, 1997 (S-01 3) and October 1998 (S-014) as the implementation dates for the changes.

We have completed the review of these applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted labeling (package insert submitted March 3 1, 1997 and November 23,1998) with the revisions listed below.Accordingly, the supplemental applications are approved effective on the date of this letter.The revisions are as follows:

Add the following last subsection in the "Warnings"section:

ULTRA Rapid Opioid Withdrawal:
Safe use of REVIA in rapid opiate detoxification programs has not been established (see ADVERSE REACTIONS).

Add the following last paragraph, in the "PRECAUTIONS" section under Post-Marketing Experience:

Adverse events, including withdrawal symptoms and death, have been reported with the use of REVIA (naltrexone hydrochloride) in ultra rapid opiate detoxification programs.The cause of death in these cases is not known (see WARNINGS).

Revise the "Carcinogenesis, Mutagenesis and Impairment of Fertility" section of the label to read as follows:
The following statements are based on the results of experiments in mice and rats- ~~form appreciable quantities of the major human metabolite, 6-β-naltrexol. Thus,~~ The potential carcinogenic, mutagenic and fertility effects of the metabolite **6-β-naltrexol are unknown.**

In a two-year carcinogenicity study in rats, there were small increases in the numbers of testicular mesotheliomas in males and tumors of vascular origin in males and females.The incidence of mesothelioma in males given naltrexone at a dietary dose of 100 mg/kg/day **(**~~59~~ 600 **mg/m^2/day**; 16 times the recommended therapeutic dose, based on body surface area) was 6%, compared with a maximum historical incidence of 4%.The incidence of vascular tumors in males and females given dietary doses of 100 mg/kg/day **(**~~59~~ 600 **mg/m^2/day)** was 4% but only the incidence in females was increased compared with a maximum historical control incidence of 2%.There was

no evidence of carcinogenicity in a two-year dietary study with naltrexone in male and female mice.

There was limited evidence of a weak genotoxic effect of naltrexone in one gene mutation assay in a mammalian cell line, in the Drosphilia recessive lethal assay, and in non-specific DNA repair tests with E.coli However, no evidence of genotoxic potential was observed in a range of other in vitro tests, including assays for gene mutation in bacteria, yeast, or in a second mammalian cell line, a chromosomal aberration assay, and an assay for NDA DNA damage in human cells. Naltrexone did not exhibit clastogenicity in an in vivo mouse micronucleus assay.

Naltrexone (100 mg/kg/day **[~~59~~ 600 mg/m²/day]** PO; 16 times the recommended therapeutic dose, based on body surface area) caused a significant increase in pseudopregnancy in the rat. A ~~descrease~~ decrease in the pregnancy rate of mated female rats also occurred. There was no effect on male fertility at this dose level. The relevance of these observations to human fertility is not known.

Under the **"Pregnancy:"** Category C section, the beginning of this section should conform to the format and wording indicated in 2 1 CFR §201 .57.

In addition, revise the **"Pregnancy"** section of the label to read as follows:
Category C. The following statements based on the results of experiments in rats- ~~form appreciable quantities of the major human metabolite, 6-β-naltrexol. Thus,~~ The potential reproductive toxicity of the metabolite **6-β-naltrexol** in rats is not known.

Naltrexone increased the incidence of early fetal loss when administered to rats in oral doses **≥30 mg/kg/day (~~18~~** 180 **mg/m²/day; 5** times the recommended therapeutic dose, based on body surface area) and to rabbits at oral doses **≥60** mg/kg/day (-69 720 **mg/m²/day;** 18 times the recommended therapeutic dose, based on body surface area). There was no evidence of teratogenicity when naltrexone was administered orally to rats and rabbits during the period of major organogenesis at doses up to 200 mg/kg/day (-32 and ~~59~~ 65 times the recommended therapeutic dose, respectively, based on body surface area).

"HOW SUPPLIED" section:
~~Delete, Store at controlled room temperature (59°-86°F, 15°-30°C)~~
~~Dispense in tight container as defined in the USP.~~

Revise storage statement as follows: Store at **25°C,** with brief excursions permitted between 15°C and 30°C **(59°-86°F),** controlled room temperature, see USP.

These revisions are terms of the supplemental NDA approval

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed.Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 18-932/S-01 3 and S-014".Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Tony Chite, P.D., Consumer Safety Officer, at (301) 827-7410.

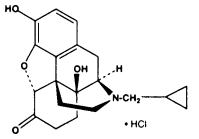
Sincerely,

Cynthia G. McCormick MD

Cynthia G. McCormick, M.D.
Director
Division of Anesthetic, Critical Care, and Addiction
Drug Products, HFD- 170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

REVIA®
(naltrexone hydrochloride tablets)

DESCRIPTION: REVIA (naltrexone hydrochloride), an opioid antagonist, is a synthetic congener of oxymorphone with no opioid agonist properties. Naltrexone differs in structure from oxymorphone in that the methyl group on the nitrogen atom is replaced by a cyclopropylmethyl group. REVIA is also related to the potent opioid antagonist, naloxone, or n-allylnoroxymorphone.



naltrexone hydrochlonde

REVIA is a white, crystalline compound. The hydrochloride salt is soluble in water to the extent of about 100 mg/mL. REVIA is available in scored film-coated tablets containing 50 mg of naltrexone hydrochloride.

REVIA Tablets also contain: lactose, microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, polysorbate 80, yellow iron oxide and red iron oxide.

CLINICAL PHARMACOLOGY:

Pharmacodynamic Actions: REVIA is a pure opioid antagonist. It markedly attenuates or completely blocks, reversibly, the subjective effects of intravenously administered opioids.

When co-administered with morphine, on a chronic basis, REVIA blocks the physical dependence to morphine, heroin and other opioids.

REVIA has few, if any, intrinsic actions besides its opioid blocking properties. However, it does produce some pupillary constriction, by an unknown mechanism.

The administration of REVIA is not associated with the development of tolerance or dependence. In subjects physically dependent on opioids, REVIA will precipitate withdrawal symptomatology.

Clinical studies indicate that 50 mg of REVIA will block the pharmacologic effects of 25 mg of intravenously administered heroin for periods as long as 24 hours. Other data suggest that doubling the dose of REVIA provides blockade for 48 hours, and tripling the dose of REVIA provides blockade for about 72 hours.

REVIA blocks the effects of opioids by competitive binding (i.e., analogous to competitive inhibition of enzymes) at opioid receptors. This makes the blockade produced potentially surmountable, but overcoming full naltrexone blockade by administration of very high doses of opiates has resulted in excessive symptoms of histamine release in experimental subjects.

The mechanism of action of REVIA in alcoholism is not understood; however, involvement of the endogenous opioid system is suggested by preclinical data. REVIA, an opioid receptor antagonist, competitively binds to such receptors and may block the effects of endogenous opioids. Opioid antagonists have been shown to reduce alcohol consumption by animals, and REVIA has been shown to reduce alcohol consumption in clinical studies.

REVIA is not aversive therapy and does not cause a disulfiram-like reaction either as a result of opiate use or ethanol ingestion.

Pharmacokinetics

REVIA is a pure opioid receptor antagonist. Although well absorbed orally, naltrexone is subject to significant first pass metabolism with oral bioavailability estimates ranging from 5 to 40%. The activity of naltrexone is believed to be due to both parent and the 6-B-naltrexol metabolite. Both parent drug and metabolites are excreted primarily by the kidney (53% to 79% of the dose), however, urinary excretion of unchanged naltrexone accounts for less than 2% of an oral dose and fecal excretion is a minor elimination pathway. The mean elimination half-life (T-1/2) values for naltrexone and 6-B-naltrexol are 4 hours and 13 hours, respectively. Naltrexone and 6-B-naltrexol are dose proportional in terms of AUC and Cmax over the range of 50 to 200 mg and do not accumulate after 100 mg daily doses.

Absorption

Following oral administration, naltrexone undergoes rapid and nearly complete absorption with approximately 96% of the dose absorbed from the gastrointestinal tract. Peak plasma levels of both naltrexone and 6-B-naltrexol occur within one hour of dosing.

Distribution

The volume of distribution for naltrexone following intravenous administration is estimated to be 1350 liters. *In vitro* tests with human plasma show naltrexone to be 21% bound to plasma proteins over the therapeutic dose range.

Metabolism

The systemic clearance (after intravenous administration) of naltrexone is -3.5 L/min, which exceeds liver blood flow (-1.2 L/min). This suggests both that naltrexone is a highly extracted drug (>98% metabolized) and that extra-hepatic sites of drug metabolism exist. The major metabolite of naltrexone is 6-B-naltrexol. Two other minor metabolites are 2-hydroxy-3-methoxy-6-B-naltrexol and 2-hydroxy-3-methyl-naltrexone. Naltrexone and its metabolites are also conjugated to form additional metabolic products.

Elimination

The renal clearance for naltrexone ranges from 30-127 mL/min and suggests that renal elimination is primarily by glomerular filtration. In comparison, the renal clearance for 6-B-naltrexol ranges from 230-369 mL/min, suggesting an additional renal tubular secretory mechanism. The urinary excretion of unchanged naltrexone accounts for less than 2% of an oral dose; urinary excretion of unchanged and conjugated 6-B-naltrexol accounts for 43% of an oral dose. The pharmacokinetic profile of naltrexone suggests that naltrexone and its metabolites may undergo enterohepatic recycling.

Hepatic and Renal Impairment

Naltrexone appears to have extra-hepatic sites of drug metabolism and its major metabolite undergoes active tubular secretion (see **Metabolism** above). Adequate studies of naltrexone in patients with severe hepatic or renal impairment have not been conducted (see **PRECAUTIONS: Special Risk Patients).**

Clinical Trials:

Alcoholism:

The efficacy of REVIA as an aid to the treatment of alcoholism was tested in placebo-controlled, outpatient, double blind trials. These studies used a dose of REVIA 50 mg once daily for 12 weeks as an adjunct to social and psychotherapeutic methods when given under conditions that enhanced patient compliance. Patients with psychosis, dementia, and secondary psychiatric diagnoses were excluded from these studies.

In one of these studies, 104 alcohol-dependent patients were randomized to receive either REVIA 50 mg once daily or placebo. In this study, REVIA proved superior to placebo in measures of drinking including abstention rates (51% vs. 23%), number of drinking days, and relapse (31% vs. 60%). In a second study with 82 alcohol-dependent patients, the group of patients receiving REVIA were shown to have lower relapse rates (21% vs. 41%), less alcohol craving, and fewer drinking days compared with patients who received placebo, but these results depended on the specific analysis used.

The clinical use of REVIA as adjunctive pharmacotherapy for the treatment of alcoholism was also evaluated in a multicenter safety study. This study of 865 individuals with alcoholism included patients with comorbid psychiatric conditions, concomitant medications, polysubstance abuse and HIV disease. Results of this study demonstrated that the side effect profile of REVIA appears to be similar in both alcoholic and opioid dependent populations, and that serious side effects are uncommon.

In the clinical studies, treatment with REVIA supported abstinence, prevented relapse and decreased alcohol consumption. In the uncontrolled study, the patterns of abstinence and relapse were similar to those observed in the controlled studies. REVIA was not uniformly helpful to all patients, and the expected effect of the drug is a modest improvement in the outcome of conventional treatment.

Treatment of Opioid Addiction:

REVIA has been shown to produce complete blockade of the euphoric effects of opioids in both volunteer and addict populations. When administered by means that enforce compliance, it will produce an effective opioid blockade, but has not been shown to affect the use of cocaine or other non-opioid drugs of abuse.

There are no data that demonstrate an unequivocally beneficial effect of REVIA on rates of recidivism among detoxified, formerly opioid-dependent individuals who self-administer the drug. The failure of the drug in this setting appears to be due to poor medication compliance.

The drug is reported to be of greatest use in good prognosis opioid addicts who take the drug as part of a comprehensive occupational rehabilitative program, behavioral contract, or other compliance-enhancing protocol. REVIA, unlike methadone or LAAM (levo-alpha-acetylmethadol), does not reinforce medication compliance and is expected to have a therapeutic effect only when given under external conditions that support continued use of the medication..

Individualization of Dosage:

DO NOT ATTEMPT TREATMENT WITH REVIA UNLESS, IN THE MEDICAL JUDGEMENT OF THE PRESCRIBING PHYSICIAN, THERE IS NO REASONABLE POSSIBILITY OF OPIOID USE WITHIN THE PAST 7-10 DAYS. IF THERE IS ANY QUESTION OF OCCULT OPIOID DEPENDENCE, PERFORM A NALOXONE CHALLENGE TEST.

Treatment of Alcoholism:

The placebo-controlled studies that demonstrated the efficacy of as an adjunctive treatment of alcoholism used a dose regimen of

REVIA (naltrexone hydrochloride) 50 mg once daily for up to 12 weeks. Other dose regimens or durations of therapy were not studied in these trials.

Physicians are advised that 515% of patients taking REVIA for alcoholism will complain of non-specific side effects, chiefly gastrointestinal upset. Prescribing physicians have tried using an initial 25 mg dose, splitting the daily dose, and adjusting the time of dosing with limited success. No dose or pattern of dosing has been shown to be more effective than any other in reducing these complaints for all patients.

Treatment of Opioid Dependence:

Once the patient has been started on REVIA, 50 mg once a day will produce adequate clinical blockade of the actions of parenterally administered opioids. As with many non-agonist treatments for addiction, REVIA is of proven value only when given as part of a comprehensive plan of management that includes some measure to ensure the patient takes the medication.

A flexible approach to a dosing regimen may be employed to enhance compliance. Thus, patients may receive 50 mg of REVIA every weekday with a 100 mg dose on Saturday or patients may receive 100 mg every other day, or 150 mg every third day. Several of the clinical studies reported in the literature have employed the following dosing regimen: 100 mg on Monday, 100 mg on Wednesday, and 150 mg on Friday. This dosing schedule appeared to be acceptable to many REVIA patients successfully maintaining their opioid-free state.

Experience with the supervised administration of a number of potentially hepatotoxic agents suggests that supervised administration and single doses of REVIA higher than 50 mg may have an associated increased risk of hepatocellular injury, even though three-times a week dosing has been well tolerated in the addict population and in initial clinical trials in alcoholism. Clinics using this approach should balance the possible risks against the probable benefits and may wish to maintain a higher index of suspicion for drug-associated hepatitis and ensure patients are advised of the need to report non-specific abdominal complaints (see **Information for Patients).**

INDICATIONS AND USAGE: REVIA is indicated:

In the treatment of alcohol dependence and for the blockade of the effects of exogenously administered opioids.

REVIA has not been shown to provide any therapeutic benefit except as part of an appropriate plan of management for the addictions.

CONTRAINDICATIONS: REVIA is contraindicated in:

1) Patients receiving opioid analgesics.
2) Patients currently dependent on opioids.
3) Patients in acute opioid withdrawal (see **WARNINGS).**
4). Any individual who has failed the naloxone challenge test or who has a positive urine screen for opioids.
5) Any individual with a history of sensitivity to REVIA or any other components of this product. It is not known if there is any cross-sensitivity with naloxone or the phenanthrene containing opioids.
6) Any individual with acute hepatitis or liver failure.

WARNINGS:

Hepatotoxicity:

REVIA has the capacity to cause hepatocellular injury when given in excessive doses.

REVIA is contraindicated in acute hepatitis or liver failure, and its use in patients with active liver disease must be carefully considered in light of its hepatotoxic effects.

The margin of separation between the apparently safe dose of REVIA and the dose causing hepatic injury appears to be only five-fold or less. REVIA does not appear to be a hepatotoxin at the recommended doses.

Patients should be warned of the risk of hepatic injury and advised to stop the use of REVIA and seek medical attention if they experience symptoms of acute hepatitis.

Evidence of the hepatotoxic potential of REVIA is derived primarily from a placebo controlled study in which REVIA was administered to obese subjects at a dose approximately five-fold that recommended for the blockade of opiate receptors (300 mg per day). In that study, 5 of 26 REVIA recipients developed elevations of serum transaminases (i.e., peak ALT values ranging from a low of 121 to a high of 532; or 3 to 19 times their baseline values) after three to eight weeks of treatment. Although the patients involved were generally clinically asymptomatic and the transaminase levels of all patients on whom follow-up was obtained returned to (or toward) baseline values in a matter of weeks, the lack of any transaminase elevations of similar magnitude in any of the 24 placebo patients in the same study is persuasive evidence that REVIA is a direct (i.e., not idiosyncratic) hepatotoxin.

This conclusion is also supported by evidence from other placebo controlled studies in which exposure to REVIA at doses above the amount recommended for the treatment of alcoholism or opiate blockade (50 mg/day) consistently produced more numerous and more significant elevations of serum transaminases than did placebo. Transaminase elevations in 3 of 9 patients with Alzheimer's Disease who received REVIA (at doses up to 300 mg/day) for 5 to 8 weeks in an open clinical trial have been reported.

Although no cases of hepatic failure due to REVIA administration have ever been reported, physicians are advised to consider this as a possible risk of treatment and to use the same care in prescribing REVIA as they would other drugs with the potential for causing hepatic injury.

Unintended Precipitation of Abstinence:

To prevent occurrence of an acute abstinence syndrome, or exacerbation of a pre-existing subclinical abstinence syndrome, patients must be opioid-free for a minimum of 7-10 days before starting REVIA. **Since the absence of an opioid drug in the urine is often not sufficient proof that a patient is opioid-free, a naloxone challenge should be employed if the prescribing physician feels there is a risk of precipitating a withdrawal reaction following administration of** REVIA. **The naloxone challenge test is described in the** DOSAGE AND ADMINISTRATION section.

Attempt to Overcome Blockade:

While REVIA is a potent antagonist with a prolonged pharmacologic effect (24 to 72 hours), the blockade produced by REVIA is surmountable. This is useful in patients who may require analgesia, but poses a potential risk to individuals who attempt, on their own, to overcome the blockade by administering large amounts of exogenous opioids. Indeed, any attempt by a patient to overcome the antagonism by taking opioids is very dangerous and may lead to a fatal overdose. Injury may arise because the plasma concentration of exogenous opioids attained immediately following their acute administration may be sufficient to overcome the competitive receptor blockade. As a consequence, the patient may be in immediate danger of suffering life endangering opioid intoxication (e.g., respiratory arrest, circulatory collapse). Patients should be told of the serious consequences of trying to overcome the opiate blockade (see **Information for Patients).**

There is also the possibility that a patient who had been treated with naltrexone will respond to lower doses of opioids than previously used, particularly if taken in such a manner that high plasma concentrations remain in the body beyond the time that naltrexone exerts its therapeutic effects. This could result in potentially life-threatening opioid intoxication (respiratory compromise or arrest, circulatory collapse, etc.). Patients should be aware that they may be more sensitive to lower doses of opioids after naltrexone treatment is discontinued.

Ultra Rapid Opioid Withdrawal:

Safe use of REVIA in ultra rapid opiate detoxification programs has not **been established (see ADVERSE REACTIONS).**

PRECAUTIONS:

General:

When Reversal of REVIA **Blockade is Required:** In an emergency situation in patients receiving fully blocking doses of REVIA, a suggested plan of management is regional analgesia, conscious sedation with a benzodiazepine, use of non-opioid analgesics or general anesthesia.

In a situation requiring opioid analgesia, the amount of opioid required may be greater than usual, and the resulting respiratory depression may be deeper and more prolonged.

A rapidly acting opioid analgesic which minimizes the duration of respiratory depression is preferred. The amount of analgesic administered should be titrated to the needs of the patient. Non-receptor mediated actions may occur and should be expected (e.g., facial swelling, itching, generalized erythema, or bronchoconstriction) presumably due to histamine release.

Irrespective of the drug chosen to reverse REVIA blockade, the patient should be monitored closely by appropriately trained personnel in a setting equipped and staffed for cardiopulmonary resuscitation.

Accidentally Precipitated Withdrawal: Severe opioid withdrawal syndromes precipitated by the accidental ingestion of REVIA have been reported in opioid-dependent individuals. Symptoms of withdrawal have usually appeared within five minutes of ingestion of REVIA and have lasted for up to 48 hours. Mental status changes including confusion, somnolence and visual hallucinations have occurred. Significant fluid losses from vomiting and diarrhea have required intravenous fluid administration. In all cases patients were closely monitored and therapy with non-opioid medications was tailored to meet individual requirements.

Use of REVIA does not eliminate or diminish withdrawal symptoms. If REVIA is initiated early in the abstinence process, it will not preclude the patient's experience of the full range of signs and symptoms that would be experienced if REVIA had not been started. Numerous adverse events are known to be associated with withdrawal.

Special Risk Patients:

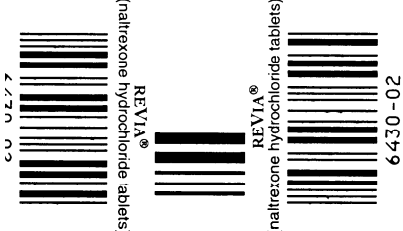
Renal Impairment: REVIA and its primary metabolite **are excreted primarily in the** urine, and caution is recommended in administering the drug to patients with renal impairment.

Hepatic Impairment: Cautions should be exercised when naltrexone hydrochloride is administered to patients with liver disease. An increase in naltrexone AUC of approximately and 10-fold in patients with compensated and decompensated liver cirrhosis, respectively, compared with subjects with normal liver function has been reported. These data also suggest that alterations in naltrexone bioavailability are related to liver disease severity.

Suicide: The risk of suicide is known to be increased in patients with substance abuse with or without concomitant depression. This risk is not abated by treatment with REVIA (see **ADVERSE REACTIONS).**

Information for Patients: It is recommended that the prescribing physician relate the following information to patients being treated with REVIA:

You have been prescribed REVIA as part of the comprehensive treatment for your alcoholism or drug dependence. You should carry



identification to alert medical personnel to the fact that you are taking REVIA (naltrexone hydrochloride). A REVIA medication card may be obtained from your physician and can be used for this purpose. Carrying the identification card should help to ensure that you can obtain adequate treatment in an emergency. If you require medical treatment, be sure to tell the treating physician that you are receiving REVIA therapy.

You should take REVIA as directed by your physician. If you attempt to self-administer heroin or any other opiate drug, in small doses while on REVIA, you will not perceive any effect. Most important, however, if you attempt to self-administer large doses of heroin or any other opioid while on REVIA, you may die or sustain serious injury, including coma.

REVIA is well-tolerated in the recommended doses, but may cause liver injury when taken in excess or in people who develop liver disease from other causes. If you develop abdominal pain lasting more than a few days, white bowel movements, dark urine, or yellowing of your eyes, you should stop taking REVIA immediately and see your doctor as soon as possible.

Laboratory Tests A high index of suspicion for drug-related hepatic injury is critical if the occurrence of liver damage induced by REVIA is to be detected at the earliest possible time. Evaluations, using appropriate batteries of tests to detect liver injury are recommended at a frequency appropriate to the clinical situation and the dose of REVIA.

REVIA does not interfere with thin-layer, gas-liquid, and high pressure liquid chromatographic methods which may be used for the separation and detection of morphine, methadone or quinine in the urine. REVIA may or may not interfere with enzymatic methods for the detection of opioids depending on the specificity of the test. Please consult the test manufacturer for specific details.

Drug Interactions: Studies to evaluate possible interactions between REVIA and drugs other than opiates have not been performed. Consequently, caution is advised if the concomitant administration of REVIA and other drugs is required.

The safety and efficacy of concomitant use of REVIA and disulfiram is unknown, and the concomitant use of two potentially hepatotoxic medications is not ordinarily recommended unless the probable benefits outweigh the known risks.

Lethargy and somnolence have been reported following doses of REVIA and thioridazine.

Patients taking REVIA may not benefit from opioid containing medicines, such as cough and cold preparations, antidiarrheal preparations, and opioid analgesics. In an emergency situation when opioid analgesia must be administered to a patient receiving REVIA, the amount of opioid required may be greater than usual, and the resulting respiratory depression may be deeper and more prolonged (see PRECAUTIONS).

Carcinogenesis, Mutagenesis and Impairment of Fertility Carcinogenicity studies in rats and mice were conducted at doses as high as 100 times the human dose. There was no statistically significant increase in the incidence of any tumors and, except for vascular tumors in the REVIA-treated female rats, the incidence of tumors observed in the studies were within ranges seen in historical control groups. REVIA was negative in bacterial and cultured mammalian cell mutation, *in vitro* chromosome aberration, and *in vivo* micronucleus, chromosome aberration, and heritable translocation assays. It was weakly positive in the *Drosophila melanogaster* recessive lethal test and gave equivocal responses in E. coli DNA repair and in *in vitro* mammalian cell mutation and anaphase chromosome assays. Overall, the study results indicate that the genotoxic potential of REVIA is low. REVIA (100 mg/kg, approximately 100 times the human therapeutic dose) caused an increase in pseudopregnancy and a decrease in the pregnancy rate of female rats. The relevance of these observations to human fertility is not known.

Pregnancy: Category C REVIA has been shown to have embryocidal and fetotoxic effects in rats and rabbits when given in dosages 30 and 60 times, respectively, the human dose.

There are no adequate and well-controlled studies in pregnant women. REVIA should be used in pregnancy only when the potential benefit justifies the potential risk to the fetus.

Labor and Delivery Whether or not REVIA affects the duration of labor and delivery is unknown.

Nursing Mothers Whether or not REVIA is excreted in human milk is unknown. Because many drugs are excreted in human milk, caution should be exercised when REVIA is administered to a nursing woman.

Pediatric Use The safe use of REVIA in pediatric patients younger than 18 years old has not been established.

ADVERSE REACTIONS: During two randomized, double-blind placebo-controlled 12 week trials to evaluate the efficacy of REVIA as an adjunctive treatment of alcohol dependence, most patients tolerated REVIA well. In these studies, a total of 93 patients received REVIA at a dose of 50 mg once daily. Five of these patients discontinued REVIA because of nausea. No serious adverse events were reported during these two trials.

While extensive clinical studies evaluating the use of REVIA in detoxified, formerly opioid-dependent individuals failed to identify any single, serious untoward risk of REVIA use, placebo-controlled studies employing up to five-fold higher doses of REVIA (up to 300 mg per day) than that recommended for use in opiate receptor blockade have shown that REVIA causes hepatocellular injury in a substantial proportion of patients exposed at higher doses (see WARNINGS and PRECAUTIONS: Laboratory Tests).

Aside from this finding, and the risk of precipitated opioid withdrawal, available evidence does not incriminate REVIA, used at any dose, as a cause of any other serious adverse reaction for the patient who is "opioid free." It is critical to recognize that REVIA can precipitate or exacerbate abstinence signs and symptoms in any individual who is not completely free of exogenous opioids.

Patients with addictive disorders, especially opioid addiction, are at risk for multiple numerous adverse events and abnormal laboratory findings, including liver function abnormalities. Data from both controlled and observational studies suggest that these abnormalities, other than the dose-related hepatotoxicity described above, are not related to the use of REVIA.

Among opioid free individuals, REVIA administration at the recommended dose has not been associated with a predictable profile of serious adverse or untoward events. However, as mentioned above, among individuals using opioids, REVIA may cause serious withdrawal reactions (see CONTRAINDICATIONS, WARNINGS, DOSAGE AND ADMINISTRATION).

Reported Adverse Events

REVIA has not been shown to cause significant increases in complaints in placebo-controlled trials in patients known to be free of opioids for more than 7-10 days. Studies in alcoholic populations and in volunteers in clinical pharmacology studies have suggested that a small fraction of patients may experience an opioid withdrawal-like symptom complex consisting of tearfulness, mild nausea, abdominal cramps, restlessness, bone or joint pain, myalgia, and nasal symptoms. This may represent the unmasking of occult opioid use, or it may represent symptoms attributable to naltrexone. A number of alternative dosing patterns have been recommended to try to reduce the frequency of these complaints (see **Individualization of Dosage).**

Alcoholism:

In an open label safety study with approximately 570 individuals with alcoholism receiving REVIA, the following new-onset adverse reactions occurred in 2% or more of the patients: nausea (10%), headache (7%), dizziness (4%), nervousness (4%), fatigue (4%), insomnia (3%), vomiting (3%), anxiety (2%) and somnolence (2%).

Depression, suicidal ideation, and suicidal attempts have been reported in all groups when comparing naltrexone, placebo, or controls undergoing treatment for alcoholism.

	RATE RANGES OF NEW ONSET EVENTS	
	Naltrexone	Placebo
Depression	0-15%	0- 17%
Suicide Attempt/Ideation	0-1%	

Although no causal relationship with REVIA is suspected, physicians should be aware that treatment with REVIA does not reduce the risk of suicide in these patients (see PRECAUTIONS).

Opioid Addiction:

The following adverse reactions have been reported both at baseline and during the REVIA clinical trials in opioid addiction at an incidence rate of more than 10%:

Difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea and/or vomiting, low energy, joint and muscle pain, and headache.

The incidence was less than 10% for:

Loss of appetite, diarrhea, constipation, increased thirst, increased energy, feeling down, irritability, dizziness, skin rash, delayed ejaculation, decreased potency, and chills.

The following events occurred in less than 1% of subjects:

Respiratory nasal congestion, itching, rhinorrhea, sneezing, sore throat, excess mucus or phlegm, sinus trouble, heavy breathing, hoarseness, cough, shortness of breath.
Cardiovascular nose bleeds, phlebitis, edema, increased blood pressure, non-specific ECG changes, palpitations, tachycardia.
Gastrointestinal excessive gas, hemorrhoids, diarrhea, ulcer.
Musculoskeletal painful shoulders, legs or knees; tremors, twitching.
Genitourinary increased frequency of, or discomfort during, urination; increased or decreased sexual interest.
Dermatologic oily skin, pruritus, acne, athlete's foot, cold sores, alopecia.
Psychiatric depression, paranoia, fatigue, restlessness, confusion, disorientation, hallucinations, nightmares, bad dreams.
Special senses eyes-blurred, burning, light sensitive, swollen, aching, strained; ears-"clogged", aching, tinnitus.
General increased appetite, weight loss, weight gain, yawning, somnolence, fever, dry mouth, head "pounding", inguinal pain, swollen glands, "side" pains, cold feet, "hot spells."

Post-marketing Experience Data collected from post-marketing use of REVIA show that most events usually occur early in the course of drug therapy and are transient. It is not always possible to distinguish these occurrences from those signs and symptoms that may result from a withdrawal syndrome. Events that have been reported include anorexia, asthenia, chest pain, fatigue, headache, hot flushes, malaise, changes in blood pressure, agitation, dizziness, hyperkinesia, nausea, vomiting, tremor, abdominal pain, diarrhea, elevations in liver enzymes or bilirubin, hepatic function abnormalities or hepatitis, palpitations, myalgia, anxiety, confusion, euphoria, hallucinations, insomnia, nervousness, somnolence, abnormal thinking, dyspnea, rash, increased sweating, and vision abnormalities.

Depression, suicide, attempted suicide and suicidal ideation have been reported in the post-marketing experience with REVIA used in the treatment of opioid dependence. No causal relationship has been demonstrated. In the literature, endogenous opioids have been theorized to

contribute to a variety of conditions. In some individuals the use of opioid antagonists has been associated with a change in baseline levels of some hypothalamic, pituitary, adrenal, or gonadal hormones. The clinical significance of such changes is not fully understood.

Adverse events, including withdrawal symptoms and death, have been reported with the use of REVIA (naltrexone hydrochloride) in ultra rapid opiate detoxification programs. No causal relationship between REVIA and these deaths has been established (see **WARNINGS).**

Laboratory Tests: With the exception of liver test abnormalities (see **WARNINGS** and PRECAUTIONS), results of laboratory tests, like adverse reaction reports, have not shown consistent patterns of abnormalities that can be attributed to treatment with REVIA.

Idiopathic thrombocytopenic purpura was reported in one patient who may have been sensitized to REVIA in a previous course of treatment with REVIA. The condition cleared without sequelae after discontinuation of REVIA and corticosteroid treatment.

DRUG ABUSE AND DEPENDENCE:

REVIA is a pure opioid antagonist. It does not lead to physical or psychological dependence. Tolerance to the opioid antagonist effect is not known to occur.

OVERDOSAGE:

There is limited clinical experience with REVIA overdosage in humans. In one study, subjects who received 800 mg daily REVIA for up to one week showed no evidence of toxicity.

In the mouse, rat and guinea pig, the oral LD_{50}s were 1,100-l ,550 mg/kg; 1,450 mg/kg; and 1,490 mg/kg; respectively. High doses of REVIA (generally ≥ 1,000 mg/kg) produced salivation, depression/reduced activity, tremors, and convulsions. Mortalities in animals due to high-dose REVIA administration usually were due to clonic-tonic convulsions and/or respiratory failure.

Treatment of Overdosage: In view of the lack of actual experience in the treatment of REVIA overdose, patients should be treated symptomatically in a closely supervised environment. Physicians should contact a poison control center for the most up-to-date information.

DOSAGE AND ADMINISTRATION:

IF THERE IS ANY QUESTION OF OCCULT OPIOID DEPENDENCE, PERFORM A NALOXONE CHALLENGE TEST AND DO NOT INITIATE REVIA THERAPY UNTIL THE NALOXONE CHALLENGE IS NEGATIVE.

Treatment of Alcoholism:

A dose of **50** mg once daily is recommended for most patients (see **Individualization of Dosage).** The placebo-controlled studies that demonstrated the efficacy of REVIA as an adjunctive treatment of alcoholism used a dose regimen of REVIA 50 mg once daily for up to 12 weeks. Other dose regimens or durations of therapy were not evaluated in these trials,

A patient is a candidate for treatment with REVIA if:

- the patient is willing to take a medicine to help with alcohol dependence
- the patient is opioid free for 7-10 days
- the patient does not have severe or active liver or kidney problems (Typical guidelines suggest liver function tests no greater than 3 times the upper limits of normal, and bilirubin normal.)
- the patient is not allergic to REVIA, and no other contraindications are present

Refer to **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS** Sections for additional information,

REVIA should be considered as only one of many factors determining the success of treatment of alcoholism. Factors associated with a good outcome in the clinical trials with REVIA were the type, intensity, and duration of treatment; appropriate management of comorbid conditions; use of community-based support groups; and good medication compliance. To achieve the best possible treatment outcome, appropriate compliance-enhancing techniques should be implemented for all components of the treatment program, especially medication compliance.

Treatment of Opioid Dependence:

Initiate treatment with REVIA using the following guidelines:

1. Treatment should not be attempted unless the patient has remained opioid-free for at least 7-10 days. Self-reporting of abstinence from opioids in opioid addicts should be verified by analysis of the patient's urine for absence of opioids. The patient should not be manifesting withdrawal signs or reporting withdrawal symptoms.
2. If there is any question of occult opioid dependence, perform a naloxone challenge test. If signs of opioid withdrawal are still observed following naloxone challenge, treatment with REVIA should not be attempted. The naloxone challenge can be repeated in 24 hours,
3. Treatment should be initiated carefully, with an initial dose of 25 mg of REVIA. If no withdrawal signs occur, the patient may be started on 50 mg a day thereafter.

Naloxone Challenge Test: The naloxone challenge test should not be performed in a patient showing clinical signs or symptoms of opioid withdrawal, or in a patient whose urine contains opioids. The naloxone challenge test may be administered by either the intravenous or subcutaneous routes.

Intravenous:

Inject 0.2 mg naloxone.
Observe for 30 seconds for signs or symptoms of withdrawal.
If no evidence of withdrawal, inject 0.6 mg of naloxone.
Observe for an additional 20 minutes.

Subcutaneous:

Administer 0.8 mg naloxone.
Observe for 20 minutes for signs or symptoms of withdrawal.

Note: Individual patients, especially those with opioid dependence, may respond to lower doses of naloxone.In some cases,0.1 mg IV naloxone has produced a diagnostic response.

Interpretation of the Challenge: Monitor vital signs and observe the patient for signs and symptoms of opioid withdrawal. These may include, but are not limited to: nausea, vomiting, dysphoria, yawning, sweating, tearing, rhinorrhea, stuffy nose, craving for opioids, poor appetite, abdominal cramps, sense of fear, skin erythema, disrupted sleep patterns, fidgeting, uneasiness, poor ability to focus, mental lapses, muscle aches or cramps, pupillary dilation, piloerection, fever, changes in blood pressure, pulse or temperature, anxiety, depression, irritability, back ache, bone or joint pains, tremors, sensations of skin crawling or fasciculations. If signs or symptoms of withdrawal appear, the test is positive and no additional naloxone should be administered.

Warning: If the test is positive, do NOT initiate REVIA therapy. Repeat the challenge in 24 hours. If the test is negative, REVIA therapy may be started if no other contraindications are present. If there is any doubt about the result of the test, hold REVIA and repeat the challenge in 24 hours.

Alternative Dosing Schedules:

Once the patient has been started on REVIA, 50 mg every 24 hours will produce adequate clinical blockade of the actions of parenterally administered opioids (i.e., this dose will block the effects of a 25 mg intravenous heroin challenge). A flexible approach to a dosing regimen may need to be employed in cases of supervised administration. Thus, patients may receive 50 mg of REVIA every weekday with a 100 mg dose on Saturday, 100 mg every other day, or 150 mg every third day. The degree of blockade produced by REVIA may be reduced by these extended dosing intervals.

There may be a higher risk of hepatocellular injury with single doses above 50 mg, and use of higher doses and extended dosing intervals should balance the possible risks against the probable benefits (see **WARNINGS** and **Individualization of Dosage).**

Patient Compliance: REVIA should be considered as only one of many factors determining the success of treatment. To achieve the best possible treatment outcome, appropriate compliance-enhancing techniques should be implemented for all components of the treatment program, including medication compliance.

HOW SUPPLIED:

REVIA (naltrexone hydrochloride) tablets are available in pale yellow 50 mg capsule-shaped film-coated tablets, scored and imprinted with "DuPont" on one side and "11" on the other, as follows:

Bottles of 30 Tablets	NDC 0056-001 l-30
Bottles of 100 Tablets	NDC 0056-001 l-70

Store at controlled room temperature (59°-86°F,15°-30°C).

Dispense in a tight container as defined in the USP.

$R_{X\ only}$

DuPont Pharma
Wilmington, Delaware 19880

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